

NCPDP Recommendations for Improved Prescription Container Labels for Medicines Containing Acetaminophen

Version 1.0

This paper provides the healthcare industry, in particular the pharmacy sector, with historical and background information on the patient risks associated with hidden sources of acetaminophen and recommendations for best practices to mitigate those risks through best practices in product labeling.

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Executive Summary

In November 2010, the National Council for Prescription Drug Programs (NCPDP) approved a project to provide standard best practices and guidance for prescription container labels of acetaminophen-containing medicines. This project was assigned to the NCPDP Professional Pharmacy Services Work Group (WG10). The Work Group formed the “Acetaminophen Best Practices Task Group” to produce this white paper, “NCPDP Recommendations for Improved Prescription Container Labels for Medicines Containing Acetaminophen.”

All stakeholders involved in the generation of prescription container labels and the dispensing of prescription medicines, as well as all stakeholders who currently play a critical role in educating healthcare professionals, consumers and patients on appropriate use of medicines are audiences for this white paper.

Acetaminophen is one of the most commonly used and most important medicines in the United States (US). When used according to the label directions, it has a well-established record of safety and efficacy. Although acetaminophen overdose is very rare in the context of its broad usage, overdose can be toxic and lead to acute liver failure.

Despite ongoing regulatory and educational efforts over the past several years to improve patient safety, intentional and unintentional acetaminophen overdose remains a significant public health problem.

Lack of patients’ awareness regarding the content of their acetaminophen-containing prescription medicines has been identified as a contributing factor to unintentional overdose. Unclear prescription labels have been cited to be root causes for medication errors, as patients may unintentionally misuse a prescribed medicine due to improper understanding of instructions. In the case of acetaminophen-containing medicines, prescription container labels often list “APAP,” or an abbreviation or truncated version of acetaminophen that most patients don’t realize is used to represent acetaminophen.

The US Food and Drug Administration (FDA) regulation requires complete spelling of “acetaminophen” as well as a standard concomitant use and liver warning on the labels of all acetaminophen-containing over-the-counter (OTC) medicines. Without clear prescription labels, patients may take more than one medicine that contains acetaminophen without realizing they may be taking a potentially harmful overdose.

The recommendations in this white paper aim to improve prescription labeling practices by harmonizing with the labeling that already exists for OTC medicines that contain acetaminophen. A patient-centered approach is needed to make the messaging consistent and strengthen and reinforce the messaging for patients across all acetaminophen-containing medicines.

NCPDP Recommendations for Improved Prescription Container Labels
for Medicines Containing Acetaminophen

NCPDP Recommendations for Improved Prescription Container Labels for Medicines Containing Acetaminophen	
1	Complete Spelling of Active Ingredients in Acetaminophen-containing Prescription Medicines <ul style="list-style-type: none"> • Completely spell all active ingredients in acetaminophen-containing medicine on the prescription labels. No acronyms, abbreviations, or truncations for acetaminophen or any other active ingredients should be used. • When a brand or branded generic medicine is dispensed, completely spell all active ingredients in addition to the branded name.
2	Acetaminophen Concomitant Use and Liver Warning Label <ul style="list-style-type: none"> • Collaborate to adopt one standard concomitant use and liver warning label in alignment with the OTC acetaminophen warnings on Drug Facts labels. This will make the messaging consistent and strengthen and reinforce the messaging for patients across all acetaminophen-containing medicines. • Adopt a standard hierarchy for the key messages on the warning label for these labels. • Delete all warning labels containing similar key messages from warning label data files to prevent duplication of key messages on prescription labels.
3	Recommendation: Prioritization of Warning Label Printing <ul style="list-style-type: none"> • Prioritize the standard warning label to print within the top three warning labels to increase the probability the label will print and be applied to prescription containers.
4	Recommendation: Icons on Pharmacy Warning Labels <ul style="list-style-type: none"> • Icons can be used on warning labels if testing has proven the icons improve consumer and patient understanding beyond simple explicit text alone. • Manufacturers of acetaminophen-containing medicines, working through Consumer Healthcare Products Association (CHPA) and in collaboration with academia, are currently conducting research to explore the effectiveness of an acetaminophen-ingredient icon for cross-industry inclusion on both OTC (Drug Facts label) and prescription container labels.
5	Recommendation: Patient-Centered Pharmacy Warning Labels <ul style="list-style-type: none"> • Employ general health literacy and plain language principles on the warning label to promote patient readability and understanding. • Patient-centered labels should reflect strategies (simple, clear language; font type and size) that promote optimal readability of critical information, consistent with recommendations by health literacy experts, plain language experts, and other organizations that have addressed patient-centered approaches to labeling in order to maximize readability and patient comprehension.

Stakeholder Call to Action:

Adopt, Implement, Adhere, Communicate and Educate

The NCPDP Acetaminophen Best Practices Task Group Call to Action is first and foremost directed to all pharmacy system stakeholders to:

- Adopt, implement and adhere to the recommendations in this white paper.
- Dialogue with pharmacy system stakeholders and those stakeholders that play a key role in consumer and patient education regarding appropriate use of medicines, with the aim to,
- Explore innovative patient-centered communication and education solutions that target and encourage pharmacist-to-patient conversations and education at point-of-dispensing and point-of-use, utilizing their state of the art clinical decision-support module systems.

Conclusions

Even though rare in the context of its widespread use, liver injury from acetaminophen overdose remains a serious public health problem. To improve patients' appropriate use of acetaminophen-containing medicines and patient safety, consumers and patients need to be able to recognize when their medicines contain acetaminophen. This will enable them to identify and compare active ingredients on all their medicines and avoid taking two medicines that contain acetaminophen simultaneously.

Voluntary efforts by the pharmacy system industry to improve prescription container labels for acetaminophen-containing medicine will not only provide consistency across OTC and prescription container labels but also across state lines, decreasing the variability that results when states take individual regulatory paths to standardization. Harmonization with existing standards and recommendations can help the pharmacy system industry implement labeling and potentiate other ongoing efforts to improve the safety of using acetaminophen-containing medicines.

Improving current prescription labeling of acetaminophen-containing medicine needs to be a priority and implementation of the recommendations in this white paper is the essential first step.

The next steps for these NCPDP recommendations are:

- Development of an NCPDP strategy for dissemination to engage all key stakeholders.
- Syndication to all stakeholders who currently play a critical role in educating healthcare professionals, consumers and patients on appropriate use of medicines.
- Harmonization with efforts of other stakeholders to optimize healthcare professional, consumer and patient communication.
- Dialogue among all stakeholders (pharmacy system stakeholders and others) to find synergies to utilize existing programs and collaborate on future initiatives.

1. Audience

The audience includes all stakeholders involved in the generation of prescription container labels and the dispensing of prescription medicines, including electronic drug database publishers, commercial and proprietary pharmacy system software companies (also known as “pharmacy practice management companies”), warning label companies and pharmacies. Also included are all stakeholders who currently play a critical role in educating healthcare professionals, consumers and patients on appropriate use of medicines.

2. Purpose

The purpose is to provide best practices and guidance for improved pharmacy-generated prescription container labels on medicines containing acetaminophen.

Improved labels will help patients 1) identify when their prescription medicines contain acetaminophen, 2) compare active ingredients on their prescription and over-the-counter (OTC) medicine labels and 3) avoid unintentional overdose.

Recommendations for developing prescription container labels in a patient-centered manner include:

- Complete spelling of acetaminophen and all other active ingredients on prescription labels, and
- The standardization of a concomitant use and liver damage warning label.

This white paper addresses only prescription labels for acetaminophen-containing medicines.

The National Council for Prescription Drug Programs (NCPDP) will devise a white paper dissemination strategy intended to engage all key stakeholders identified as the audiences for this white paper.

3. Background

Acetaminophen is one of the most commonly used and most important medicines in the United States (US). When used according to the label directions, it has a well-established record of safety and efficacy. Although very rare in the context of its broad usage, overdose can be toxic and lead to acute liver failure.¹

Over the past several years, the US Food and Drug Administration (FDA) has taken a number of steps to impact the factors that contribute to the incidence of liver injury resulting from unintentional acetaminophen overdose. These actions include asking drug manufacturers to limit the amount of acetaminophen in prescription medicines that contain acetaminophen,² mandating updated safety information on manufacturers' labels for these medicines, updating the packaging and Drug Facts label for over-the-counter

¹ FDA Advisory Committees Meeting. *Liver Injury Related to the Use of Acetaminophen*. June 29-30, 2009. Available at: <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm143083.htm>. (accessed April 29, 2011).

² FDA. Acetaminophen Prescription Products Limited to 325 mg Per Dosage Unit: Drug Safety Communication. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm239955.htm> (accessed April 29, 2011).

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NCPDP Recommendations for Improved Prescription Container Labels
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medicines and public education efforts.³ The FDA continues to consider additional measures for increasing patients' safety.

Unclear prescription labels have been shown to be root causes for medication errors, as patients may unintentionally misuse a prescribed medicine due to improper understanding of instructions.⁴ As minimal standards and regulations exist for content and format and may vary across state lines, prescription container labels can differ between and within local and national pharmacies. The American College of Physicians Foundation (ACPF) Medication Labeling Technical Advisory Board has highlighted the importance of the container label as the most tangible and repeatedly used source of prescription drug instructions for use.^{5, 6} Lack of patients' awareness regarding the content of their acetaminophen-containing prescription medicines has been identified as a contributing factor to unintentional acetaminophen overdose. Since 2004, the FDA has taken steps to encourage state boards of pharmacy to improve prescription labels for acetaminophen-containing medicine to improve patients' ability to recognize their prescription medicines contain acetaminophen.^{7, 8}

In early 2010, the FDA's Safe Use Initiative began a dialogue with the National Association of Boards of Pharmacy (NABP) about interventions to reduce unintentional overdoses involving acetaminophen-containing prescription medicines. Extensive parallel efforts among industry, pharmacy, patient safety and healthcare professional organizations culminated in the FDA and NABP joining forces with these stakeholders with the shared goal of encouraging best practices for prescription labels of acetaminophen-containing medicines.⁹

In November 2010, the NCPDP approved a project to provide standard best practices and guidance for prescription labeling of acetaminophen-containing medicines. This project was assigned to the NCPDP Professional Pharmacy Services Work Group (WG 10). The Work Group formed the "Acetaminophen Best Practices Task Group." The first mission of the Task Group was to produce this white paper, "NCPDP Recommendations for Improved Prescription Container Labels for Medicines Containing Acetaminophen," to communicate the recommendations of the Task Group to all relevant stakeholders.

³ FDA. Final rule: Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use. Available at: <http://edocket.access.gpo.gov/2009/pdf/E9-9684.pdf> (accessed April 29, 2011) and codified in 21 CFR §201.326, Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required warnings and other labeling.

⁴ Institute of Medicine. Preventing Medication Errors: Quality Chasms Series. 2007. Washington, DC: The National Academies Press.

⁵ FDA Advisory Committees Meeting. *Liver Injury Related to the Use of Acetaminophen*. June 29-30, 2009. Available at: <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm143083.htm> (accessed April 29, 2011).

⁶ ACPF. Improving Prescription Drug Container Labeling in the United States. A Health Literacy and Medical Safety Initiative. Presented to the Institute of Medicine Roundtable on Health Literacy. October 12, 2007. Available at: <http://www.acpfoundation.org/files/medlabel/acpfwhitepaper.pdf> (accessed May 6, 2011).

⁷ Letter from Steven Galson to State Boards of Pharmacy. Acetaminophen hepatotoxicity and nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal and renal toxicity. Jan 22, 2004. Available at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM171903.pdf>. (accessed April 29, 2011).

⁸ FDA. CDER Letter to NABP: Prohibition of acetaminophen abbreviation. July 19, 2010. Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM230737.pdf> (accessed March 25, 2011).

⁹ FDA. Safe Use Initiative: Reducing harm risk from acetaminophen. *Pharmacy Today*. September 2010; 61. Available at <http://www.fda.gov/downloads/ForHealthProfessionals/ArticlesofInterest/UCM228618.pdf> (accessed May 3, 2011).

4. Rationale

Acetaminophen is considered safe when used according to the directions on the labels of acetaminophen-containing OTC and prescription medicines. However, intentional and unintentional acetaminophen overdosing remains a significant public health problem.¹⁰

In a study that combined data from 22 specialty medical centers in the United States, acetaminophen-related liver injury was the leading cause of acute liver failure for the years 1998 through 2003. Consumers and patients in this study were found to have taken too much acetaminophen from nonprescription medicines, prescription medicines, or both. Nearly half of these cases involved overdose in which the patient had not intended to take too much acetaminophen (unintentional overdoses). More than half (63%) of the unintentional overdose cases involved the use of prescription acetaminophen and narcotic combination medicines.¹¹

The following are some factors which may contribute to unintentional acetaminophen overdoses.

- Taking more than the recommended maximum daily dose of acetaminophen (4 grams/day for adults, 75 mg/kg/day for children under the age of 12 years) is an overdose. An overdose may occur if a consumer or patient takes:¹²
 - More than the labeled dose of one acetaminophen medicine, or
 - More than one medicine containing acetaminophen (eg, an OTC medicine that contains acetaminophen with a prescription medicine that contains acetaminophen).
- Acetaminophen is an active ingredient in more than 600 prescription and nonprescription medicines. IMS reports that 24 billion doses of acetaminophen-containing medicines were sold in 2010 (52% prescription and 48% OTC acetaminophen-containing dosages).¹³
 - Acetaminophen is combined with other active ingredients in prescription medicines primarily to help relieve pain.
 - Acetaminophen is used as the single ingredient in OTC medicines to help relieve pain and reduce fever and it is combined with other active ingredients in OTC medicines to treat pain, symptoms of colds, flu, allergies, and sleeplessness.

¹⁰ FDA Advisory Committees Meeting. *Liver Injury Related to the Use of Acetaminophen*. June 29-30, 2009. Available at: <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm143083.htm> (accessed April 29, 2011).

¹¹ Larson AM, et al for the Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005; 42:1364–72.

¹² FDA. Safe Use Initiative: Opportunities for Collaboration-Acetaminophen Toxicity. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm188762.htm> (accessed April 29, 2010).

¹³ IMS Health. National Sales Perspective (NSP) 2010.

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- Consumers and patients may not realize:
 - Their medicine contains the active ingredient acetaminophen.^{14, 15, 16}
 - Acetaminophen is a common ingredient in multiple OTC and prescription medicines.
 - An overdose of acetaminophen may cause liver toxicity.^{15, 17}
 - The potential adverse consequences of taking two different acetaminophen-containing medicines simultaneously and from exceeding the maximum daily dose.¹⁸
- It is difficult for patients to recognize acetaminophen as an ingredient in prescription medicines. Prescription medicines that contain acetaminophen often are not adequately labeled to identify acetaminophen as an active ingredient on prescription labels.
 - Acetaminophen often is labeled simply as “APAP” or with unclear abbreviations or truncated versions of acetaminophen (eg, ACT, acetamin) which most patients do not realize are used to represent acetaminophen.^{16, 19, 20}
 - A prescription brand or branded generic medicine that contains acetaminophen may be dispensed with only the brand or branded generic name listed on the label and no active ingredients listed.¹⁹

Without clear labels, consumers and patients may take more than one medicine that contains acetaminophen without realizing they may be taking a potentially harmful overdose.

¹⁴ Fosnocht D, et al. Emergency department patient knowledge concerning acetaminophen (paracetamol) in over-the-counter and prescription analgesics. *Emerg Med J*. 2008; 25:213-216.

¹⁵ Stumpf JL, et al. Knowledge of appropriate acetaminophen doses and potential toxicities in an adult clinical population. *J Am Pharm Assoc*. 2007; 47:1:35-41.

¹⁶ Chen L, et al. Knowledge about acetaminophen toxicity among emergency department visitors. *Vet Human Toxicol*. 2002; 44:370-73.

¹⁷ Cham E, et al. Awareness and use of over-the-counter pain medication: an emergency room survey. *South Med J*. 2002; 95(5):529-35.

¹⁸ FDA. CDER Letter to NABP: Prohibition of acetaminophen abbreviation. July 19, 2010. Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM230737.pdf> (accessed March 25, 2011).

¹⁹ Institute for Safe Medication Practices. Don't hide the acetaminophen. *Pennsylvania State Board of Pharmacy Newsletter*. Winter 2007-2008: 4-5.

²⁰ Letter from Steven Galson to State Boards of Pharmacy. Acetaminophen hepatotoxicity and nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal and renal toxicity. Jan 22, 2004. Available at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM171903.pdf> (accessed May 6, 2011).

As described in Section 5, clear labeling practices already exist for all acetaminophen-containing OTC medicines. The primary display panel and the Drug Facts label on both the carton and the container for these medicines are required to contain:²¹

- Complete spelling of “acetaminophen” and all other active ingredients
- Standardized concomitant use and liver warnings

The best practices and guidance recommended in this white paper are intended to improve prescription container labels for acetaminophen-containing medicines by aligning with the labeling that already exists for OTC medicines that contain acetaminophen.

This would include:

- The complete spelling of “acetaminophen” and any other active ingredients, eliminating the use of abbreviations, acronyms, and truncations, and
- Incorporating a standard concomitant use and liver warning label

Implementation of these recommendations is the essential first step towards making it possible for patients to identify and compare active ingredients on their prescription and OTC medicine labels and to avoid taking two medicines which contain acetaminophen simultaneously. Clear labels will also increase the success and impact of ongoing collaborative efforts to educate consumers and patients on how to safely use acetaminophen-containing medicines.

5. Regulations and Authorities: Over-the-Counter and Prescription Labels for Acetaminophen-Containing Medicines

This section describes existing regulations and authorities for the labeling of both OTC and prescription acetaminophen-containing medicines.

The recommendations provided in this white paper are made in consideration of existing regulations and authorities with the aim of improving labeling practices and harmonizing prescription and OTC labels.

5.1 Over-the-Counter Medicine Labels^{21, 22}

The current FDA OTC Drug Facts labeling standards have provided guidance in the development of the recommendations described in this white paper.

The OTC Drug Facts label regulation requires most OTC medicines to comply with format and content requirements and intends to make it easier for consumers to read and understand OTC medicine labels and use the medicines safely and effectively.

²¹ FDA. Final Rule: Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use. Available at: <http://edocket.access.gpo.gov/2009/pdf/E9-9684.pdf> (accessed April 29, 2011) and codified in 21 CFR §201.326, Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required warnings and other labeling.

²² 21 CFR §201.61 Statement of identity, §201.66 (c) (2) and (3) Format and content requirements for over-the-counter (OTC) drug product labeling and §299.4 Established names for drugs.

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In addition, a 2009 FDA regulation requires increased prominence of “acetaminophen” as an active ingredient as well as a standard concomitant use and liver warning on the Drug Facts label for all acetaminophen-containing OTC medicines.

5.1.1 Principal Display Panel

All acetaminophen-containing medicines (single ingredient and combination) must have a statement of identity and the name “acetaminophen” must appear highlighted (eg, in fluorescent or contrasting color) or in bold type and in prominent print size on the principal display panel. The highlighted printing is to make consumers aware that acetaminophen is present in the medicines they are using in an effort to prevent unintentional overdose.

5.1.2 Active Ingredient/Purpose Section

Under the “Active Ingredient” heading, the established name of each active ingredient and the quantity of each active ingredient per dosage unit is required. For acetaminophen-containing medicines, the information under the Active Ingredient and Purpose headings may appear highlighted. (In 2002, the OTC drug industry voluntarily adopted highlighting of “acetaminophen” under the “Active Ingredient/Purpose” heading on the Drug Facts label.) (See “[Appendix B. Sample Acetaminophen Drug Facts Label Excerpt](#)” for this section of the OTC Drug Facts label.)

5.1.3 Warnings

The 2009 regulation added a warning about the possibility of liver injury and a warning about concomitant use of acetaminophen-containing medicines. These new warnings are required to enhance consumer awareness and knowledge of the active ingredient. The aim is to reduce liver injury from unintentional overdosing and the incidence of adverse health outcomes. (See “[Appendix B. Sample Acetaminophen Drug Facts Label Excerpt](#)” for relevant portions of this section of the OTC Drug Facts label.)

5.1.3.1 Liver Warning²³

- **For medicines labeled for adult use only**, the liver warning states:

“Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take

- more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount [optional: `for this product']
- with other drugs containing acetaminophen
- 3 or more alcoholic drinks every day while using this product.”

This liver warning must be the first warning under the “Warnings” heading.

- **For medicines labeled only for children under 12 years of age**, and

²³ FDA. Final rule: Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use. Available at: <http://edocket.access.gpo.gov/2009/pdf/E9-9684.pdf> (accessed 29 April 2011) and codified in 21 CFR §201.326, Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required warnings and other labeling. Version 1.0

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- **For medicines labeled for adults and children under 12 years of age,**
refer to the regulation (also called the “final rule”) for the exact wording of the liver warning.

5.1.3.2 Concomitant Use Warning²⁴

- **For medicines labeled for adult use only,** the concomitant use warning states:
 - "Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.
- **For medicines labeled only for children under 12 years of age, and**
- **For medicines labeled for adults and children under 12 years of age,**

refer to the regulation (also called the “final rule”) for the exact wording of the concomitant use warning.

5.2 Prescription Drug Labeling

The labeling requirements for prescription drugs describe the required content for the manufacturers' package labels and prescription information intended primarily for healthcare professionals.²⁵ This professional label is commonly called the “package insert” or “drug label” and is one of the primary references electronic drug database publishers use to generate their data files.

In January 2011, the FDA issued a Federal Register notice and a drug safety communication to announce new measures to help make acetaminophen-containing prescription medicines safer for patients.²⁶ A new boxed warning²⁷ required for these medicines highlights the potential for severe liver injury. The drug safety communication addressed the need for healthcare professionals to educate consumers and patients about the importance of reading all prescription and OTC labels to ensure they are not taking multiple acetaminophen-containing medicines.

The FDA also asked drug manufacturers to limit the quantity of acetaminophen in prescription medicines, which are predominantly combinations of acetaminophen and opioids, to no more than 325 mg per tablet, capsule, or other dosage unit. With a reduced dosage, patients will be less likely to overdose on acetaminophen if they

²⁴ FDA. Final rule: Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use. Available at: <http://edocket.access.gpo.gov/2009/pdf/E9-9684.pdf> (accessed 29 April 2011) and codified in 21 CFR §201.326, Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required warnings and other labeling.

²⁵ 21 CFR §201 Subpart B Labeling Requirements for Prescription Drugs and/or Insulin.

²⁶ FDA. FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure. January 2011. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm> (accessed April 29, 2011), and Prescription Drug Products Containing Acetaminophen: Actions to Reduce Liver Injury from Unintentional Overdose FDA-2011-N-0021-0001, available at: <http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0021-0001> (accessed April 29, 2011).

²⁷ A warning on the package insert for a prescription medicine that the FDA requires to appear in a box. Commonly referred to as a “black box warning,” it is bolded and boxed to highlight a contraindication or serious risk associated with the medicine. For more information, see 21 CFR §201.57 (c) (1).

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mistakenly take too many doses of an acetaminophen-containing prescription medicine.²⁸

5.3 Prescription Container Labels

5.3.1 Prescription Labels

The content of prescription labels is subject to both federal and state authorities.

- Examples of federal statutes and regulations concerning prescription labels include:
 - Food, Drug and Cosmetic Act²⁹ – “Exemptions and consideration for certain drugs, devices, and biological products”
 - Controlled Substances Act – Labeling and Packaging³⁰ which includes “Statement of required warning”³¹ and “Labeling of substances and filling of prescriptions”³²
- Additional provisions are mandated by the individual state governments.

The Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy (NABP Model Act)³³ identify critical and important information for patients that must appear as well as additional information that may appear on all prescription labels.

5.3.2 Pharmacy Warning Labels

Warning labels, also referred to as “auxiliary labels” or “auxiliary warning labels,” are not standardized and are not regulated or reviewed by federal authorities. Most states offer only general guidance on warning labels and NABP does not have a policy regarding warning labels in their Model Act.³³

The Acetaminophen Best Practices Task Group conducted a survey of current warning labels for acetaminophen-containing prescription medicines to assess the content and consistency of the warning labels available in the marketplace. The labels reviewed are produced by three warning label companies and current as of March 2011. The messages on these labels can be divided into the following four categories: 1) content (informing the medicine contains acetaminophen), 2) overdose, 3) liver injury, and 4) concomitant use. (See “[Appendix A. Survey of Current Acetaminophen Warning Labels](#)” for the inventory.)

²⁸ FDA. FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure. January 2011. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm> (accessed April 29, 2011), and Prescription Drug Products Containing Acetaminophen: Actions to Reduce Liver Injury from Unintentional Overdose FDA-2011-N-0021-0001, available at: <http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0021-0001> (accessed April 29, 2011).

²⁹ 21 United States Code (USC) §353 (b) (2)

³⁰ 21 USC §825 (c)

³¹ 21 CFR §290.5

³² 21 CFR §1306.24

³³ National Association of Boards of Pharmacy (NABP). Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy (*NABP Model Act*), August 2010. Available at: <http://www.nabp.net/publications/model-act/> (accessed April 25, 2011).

Summary of Inventory

Three different combinations of the four categories were used by the companies, often in different text versions. A fourth label with a distinctly different message also was found.

- **Four messages combined on one label: content + overdose + liver injury + concomitant use** – Only one company distributes this label.
- **Three messages combined on one label: content + overdose + liver injury** – All three companies distribute the same text version of this combination label, but one adds “(paracetamol)” as a modifier of “acetaminophen.” All three companies also distribute a second text version of this combination.
- **Concomitant use message** – All three companies distribute different text versions of the concomitant use message, but include the phrase, “check all medicine labels carefully.”
- **One label displays a distinctly different message** – Two of the three companies distribute this warning label: “Do not take aspirin or acetaminophen without checking with your doctor.”

In total, eight different labels are available from the three companies surveyed. The results of the survey demonstrate at least some of the variability in warning label content currently available for acetaminophen-containing prescription medicines, including variety within individual companies. Note that the labels do not mirror the most recent warnings required on OTC acetaminophen-containing medicine labels (Section 5.1.3) or the required warnings on the prescription drug labeling (Section 5.2).

The United States Pharmacopeia (USP) proposed a new guideline for standardized patient-centered labels in General Chapter <17> in its January 2011 *Pharmacopeial Forum*. The chapter addresses the issue of warning labels, stating, “...there is great variability in the actual auxiliary warning and supplemental instructional information applied by individual practitioners to the same prescription.” USP recommended, “Evidence-based auxiliary information, both text and icons, should be standardized so that it is applied consistently and does not depend on individual practitioner choice.”³⁴

6. NCPDP Recommendations for Improved Prescription Container Labels for Medicines Containing Acetaminophen

Prescription labels on containers dispensed in pharmacies are often the sole source of information patients use when they are taking their prescription medicine.^{35, 36} Information that is critical for patients’ safe and effective use of the medicine should be prominently displayed on prescription container labels in a patient-centered manner.³⁴

³⁴ The United States Pharmacopeial Convention. General Chapter <17> - Prescription Container Labeling. *Pharmacopeial Forum*. 2011; 37:2-7. Available at: <http://www.usp.org/pdf/EN/USPNF/M5531.pdf> (accessed April 29, 2011).

³⁵ Institute of Medicine. *Standardizing medication labels: Confusing patients less*. Workshop summary. Washington DC: The National Academies Press; 2008.

³⁶ Webb J, et al. Patient-centered approach for improving prescription drug warning labels. *Patient Educ Couns*. 2008; 7:443-449. Available at: <http://dx.doi.org/10.1016/j.pec.2008.05.019> (accessed May 3, 2011).
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The recommended practices for prescription labels for acetaminophen-containing medicines aim to help decrease medication errors that result from the patient's inability to recognize acetaminophen as the active ingredient in their prescription medicine.

The Task Group acknowledges that some recommendations specified under Section 6.2 are more stringent than current NABP policy (NABP Model State Pharmacy Act and Model Rules) which calls for critical information never to be truncated, including the drug name.³⁷ Following an FDA Public Workshop called: "Public Workshop: Developing Guidance on Naming, Labeling, and Packaging Practices to Reduce Medication Errors" (June 2010), NABP released a public statement to the state boards of pharmacy recommending that they prohibit the use of "APAP" on prescription labels and to require complete spelling of acetaminophen.

6.1 Prescription Labels

6.1.1 Complete Spelling of Active Ingredients

To enable patients to recognize acetaminophen and all active ingredients in their medicines, the Task Group strongly recommends that the prescription labels **for all medicines that contain acetaminophen**, whether a brand, branded generic or generic prescription medicine is dispensed, include the following information:

- a. "Acetaminophen" and all other active ingredients should be completely spelled on the prescription label.
- b. When a brand or branded generic is dispensed, acetaminophen and all other active ingredients should be completely spelled, in addition to the brand or branded generic name of the medicine. (See "[Appendix C. Sample Acetaminophen Prescription Container Label](#)")
- c. No abbreviation, acronym, or truncated version of acetaminophen or other active ingredients should be permitted on prescription labels. The length of the drug name field on prescription labels must accommodate the complete spelling of acetaminophen and all other active ingredients.
- d. The amount of each active ingredient present in the medicine should appear clearly on the prescription label.

6.1.2 Guidance for Developing Patient-Centered Prescription Labels

In order to promote patient understanding of prescription labels for acetaminophen-containing medicines, the Task Group recommends applying general principles of health literacy and plain language when implementing the recommendations.

Use text features that increase readability and patients' reading comprehension of critical information:

- a. Use sentence case.

³⁷ National Association of Boards of Pharmacy (NABP). Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy (*NABP Model Act*), August 2010. Available at: <http://www.nabp.net/publications/model-act/> (accessed April 25, 2011).

- b. Restrict use of capital letters, all capitalized words, italics and stylized types. They slow reading. For example:
 - i. “acetaminophen” is preferred over “Acetaminophen.”
 - ii. Don’t use “ACETAMINOPHEN.”
 - iii. Use “Brandname”; don’t use “BRANDNAME.”
- c. Font size: Optimal font size for print reading is 12-14 points.

Current NABP policy recommends that critical information for patients be printed on the prescription label with emphasis (highlighted or bolded), in a sans serif typeface (such as “Arial”), minimum 12-point size and in “sentence case.”³⁸ The USP proposed standard for prescription labels recommends use of a large font size (eg, minimum 11-point Arial) for critical information.³⁹

6.2 Standard Pharmacy Warning Labels

There are currently multiple acetaminophen warning labels in use. (See Section 5.3.2, “Pharmacy Warning Labels”) In the absence of regulations for standardizing and prioritizing pharmacy warning labels, this white paper proposes that industry collaborate to adopt one standard warning label. The acetaminophen warning label should be prioritized to print within the top three warning labels. This prioritization increases the probability that this warning label will print and be applied to prescription containers. Pharmacy systems should be programmed to ensure adequate prioritization.

6.2.1 Guidance for Developing Patient-Centered Pharmacy Warning Labels

This white paper provides guidance for the hierarchy and wording of key messages that should be included on the new acetaminophen warning label through application of plain language and health literacy principles in order to:

- Align with the FDA-approved concomitant use and liver warning requirements for the OTC Drug Facts label for acetaminophen-containing OTC medicine.⁴⁰
- Promote optimal patient understanding of the warnings on warning labels while taking into account the limited space available.

³⁸ National Association of Boards of Pharmacy (NABP). Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy (*NABP Model Act*), August 2010. Available at: <http://www.nabp.net/publications/model-act/> (accessed April 25, 2011).

³⁹ The United States Pharmacopeial Convention. General Chapter <17> - Prescription Container Labeling. *Pharmacopeial Forum*. 2011; 37:2-7. Available at: <http://www.usp.org/pdf/EN/USPNF/M5531.pdf> (accessed April 29, 2011).

⁴⁰ 21 CFR §201.61 and §201.66(c)(2) and (3) Labeling requirements for Over-the-Counter Drugs. Version 1.0

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6.2.1.1 Hierarchy of Key Messages Within the Warning Label

The Task Group recommends a standard hierarchy of key messages within the warning label. This list presents the key messages in decreasing order of importance (1-4).

1. Content message – Active ingredient
2. Action and warning message – Concomitant use warning (prescription and nonprescription)
3. Risk and consequence message – Overdose and liver warning
4. Healthcare professional message – Where to address questions

6.2.1.2 Apply Plain Language and Health Literacy Principles

In order to promote patient understanding of prescription labels for acetaminophen-containing medicine, the Task Group recommends industry use general principles of health literacy and plain language when implementing the recommendations put forth in this white paper, such as those described in the Federal Plain Language Guidelines.⁴¹

Use features that increase readability and reading comprehension of critical information:

- a. Use sentence case.

Restrict use of capitalized words, all capital letters in a word, italics and stylized font types. They slow reading. Some examples are:

 - “acetaminophen” is preferred over “Acetaminophen.”
 - Don’t use “ACETAMINOPHEN.”
- b. Don’t hyphenate words between lines.
- c. Use large font size for critical information (eg, 11 point Arial).⁴²
- d. Explicitly state desired behaviors. General concepts don’t lead to action.
 - i. Use every day words, limit the use of medical and science terms and use short sentences.
 - ii. Be concise – leave out unnecessary words. Don’t use jargon or technical terms when everyday words have the same meaning.
 - iii. Use words and terms consistently throughout.⁴¹

⁴¹ Federal Plain Language Guidelines. Available at:

<http://www.plainlanguage.gov/howto/guidelines/bigdoc/index.cfm> (accessed April 25, 2011)

⁴² The United States Pharmacopeial Convention. General Chapter <17> - Prescription Container Labeling. *Pharmacopeial Forum*. 2011; 37:2-7. Available at: <http://www.usp.org/pdf/EN/USPNF/M5531.pdf> (accessed April 29, 2011).

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6.2.1.3 Recommended Language for Key Messages

	Key Message	Avoid Using:	Do Use:	Recommended Language:
1	Content	<ul style="list-style-type: none"> • All capital letters, eg, "ACETAMINOPHEN" • Capitalized words, eg, "Acetaminophen" • <i>Italics</i> and bolding • Different terms for the same thing, like drugs and medicines 	<ul style="list-style-type: none"> • No capitals or capitals for only the first letter of acetaminophen • Sentence case • Simple, familiar words, such as "has" instead of "contains" are better understood by patients 	<ul style="list-style-type: none"> • Contains acetaminophen. • This has acetaminophen.
2	Action and Warning	<ul style="list-style-type: none"> • Passive voice • Unclear statements that may confuse patients as to what they need to do to improve their safety • "Do not" • "acetaminophen-containing drugs" • Slashes (eg, prescription/nonprescription) 	<ul style="list-style-type: none"> • Active voice • Direct, clear directions for the action patients should take. Place action up front on label. • Contractions to minimize chance patients will miss the "not" • Consistent terms. "Medicines" (three syllables) is preferable to medications (4 syllables). "Drugs" may be preferred if space is restricted. • "Drugs that contain acetaminophen" or "drugs that have acetaminophen" • "or" or "and" 	<ul style="list-style-type: none"> • Don't use with other drugs that contain acetaminophen (prescription or nonprescription). • Don't take with any other medicines that have acetaminophen (prescription or nonprescription).
3	Risk and Consequence	<ul style="list-style-type: none"> • Non-descriptive or vague terms for severity or consequences that patients may not understand (eg, "liver problems") • Metric abbreviations patients may not understand (eg, "mg" or "G") • References to quantities that would require patients to do calculations (eg, "more than 4000 mg") 	<ul style="list-style-type: none"> • Language to give explicit consequences from "misbehavior" so patients understand their risks and the rationale for and importance of adherence • Use language consistent with the Drug Facts label whenever possible (eg, liver damage) 	<ul style="list-style-type: none"> • Too much can cause liver damage. • Too much acetaminophen can cause severe liver damage.
4	Healthcare professional	<ul style="list-style-type: none"> • Non-descriptive terms or titles 	<ul style="list-style-type: none"> • Active voice • Pronouns that can help personalize the message, when there's room 	<ul style="list-style-type: none"> • Questions? Ask your doctor or pharmacist. • If you have questions, ask your doctor or pharmacist.

6.2.1.4 Examples of Pharmacy Warning Labels

Three examples of a standard warning label that comply with the recommendations in this white paper, including utilizing plain language and health literacy principles, are provided.

Example 1:

Contains acetaminophen. Don't use with other drugs that contain acetaminophen (prescription or nonprescription) unless doctor approves. Too much can cause liver damage.

Example 2:

This has acetaminophen. Don't take with other medicines that have acetaminophen (prescription or nonprescription). Too much can cause liver damage. Questions? Ask your doctor or pharmacist.

Example 3:

This has acetaminophen. Don't take with any other medicines that have acetaminophen (prescription or nonprescription). Too much can cause liver damage.

Label comprehension research can help assess patient understanding of the new standard warning label.⁴³ However, a recommendation for label comprehension testing is outside of the scope of this white paper.

6.2.2 Use of Icons on the Standard Acetaminophen Pharmacy Warning Label

It is common practice for warning label companies to develop and include icons or pictograms on pharmacy warning labels. Icons can help improve patient understanding of complex health information.⁴⁴ However, as noted in the USP proposed standard for prescription labeling, patients frequently misunderstand icons. Because of the limited space on the container, the Task Group recommends using only icons when proven through testing to improve consumer and patient understanding beyond simple explicit text alone.

Evidence-based auxiliary information, both text and icons, should be standardized so that it is applied consistently and does not depend on individual practitioner choice.^{43, 45}

Manufacturers of acetaminophen-containing medicines, working through Consumer Healthcare Products Association (CHPA) and in collaboration with academia,⁴⁵ are currently conducting research to explore the effectiveness of a uniform acetaminophen-ingredient icon for cross-industry inclusion on both OTC (Drug Facts label) and

⁴³ Wolf MS, et al. Improving prescription drug warnings to promote patient comprehension. *Arch Intern Med.* 2010;170:50-57.

⁴⁴ Houts PS, et al. The role of pictures in improving health communication: A review of research on attention, comprehension, recall, and adherence. *Patient Educ Couns.* 2006; 61:173–190.

⁴⁵ King JP, et al. Developing consumer-centered, nonprescription drug labeling: a study in acetaminophen. *Am J Prev Med.* 2011;40:593–598.

prescription container labels. The goal of the acetaminophen-ingredient icon is to help consumers and patients further recognize acetaminophen as the active ingredient in their medicines. The pharmacy warning label companies have agreed to work with the OTC manufacturers to add the uniform research-based acetaminophen-ingredient icon to the standard acetaminophen warning label once its effectiveness has been confirmed in quantitative testing on both prescription and nonprescription (OTC) medicines.

6.3 Prescription Labels for Prescribed OTC Medicine

- a. Pharmacist dispenses the product in the manufacturer's original packaging:

Pharmacy staff should take care to apply the prescription label in such a way as to preserve the integrity of the critical acetaminophen safety information contained in the Drug Facts label. This includes the active ingredients, the strength, and warnings section in their entirety.

- b. Pharmacist dispenses the product in a container other than the manufacturer's original packaging:

Pharmacy staff should follow the recommendation put forth in this white paper, including the recommendation for complete spelling of all active ingredients as in Section 6.1 of this document; and the recommendation for the warning label as in Section 6.2 of this document.

7. Stakeholder Call to Action:

Adopt, Implement, Adhere, Communicate, and Educate

The NCPDP Acetaminophen Best Practices Task Group Call to Action is first and foremost directed to all pharmacy system stakeholders, as they can drive the changes required to implement best practices in pharmacy systems as described in this white paper. This section outlines a call to action to all pharmacy system stakeholders, including drug databases publishers, commercial and proprietary pharmacy system software companies, warning label companies and pharmacies, to further explore implementation of innovative patient-centered communication and education solutions that target and encourage pharmacist-to-patient conversations and education at point of dispensing, utilizing their state of the art clinical decision-support module systems.

Changing consumer and patient behaviors to encourage appropriate use of acetaminophen-containing medicines warrants a concerted effort of stakeholders to optimize communication with and education of healthcare professionals, consumers, and patients. As a first step, this white paper will be syndicated to all stakeholders who currently play a critical role in educating healthcare professionals, consumers and patients on the appropriate use of medicines.

All stakeholders are encouraged to enter into a dialogue to find synergies in utilizing existing programs and to collaborate on future initiatives.

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7.1 Pharmacy System Stakeholder Map: Call to Action, Challenges, and Opportunities

Stakeholders	Call to Action	Challenges and Opportunities
Drug Database Publishers	<ol style="list-style-type: none"> 1. Include the complete spelling of acetaminophen and all other active ingredients for acetaminophen containing combination medicines. 2. Eliminate “APAP” and abbreviations or truncated versions of acetaminophen from product names in the data files of all acetaminophen-containing medicines. 3. Provide data to support the printing of acetaminophen and all other active ingredients in addition to the brand or branded generic name of the medicine on the prescription labels. 4. Adopt one standard warning label for all acetaminophen-containing prescription medicines, utilizing the concepts presented in this white paper. (Section 6.2) <ul style="list-style-type: none"> • Standardize prioritization of print sequence for the new standard acetaminophen warning label to print among the top three pharmacy warning labels. • Delete all warning labels containing similar key messages from warning label data files to prevent duplication of key messages on prescription labels. 	<p>Complete spelling of acetaminophen and all other active ingredients</p> <ul style="list-style-type: none"> • Changes implemented by drug database publishers regarding complete spelling of acetaminophen and all other active ingredients in acetaminophen-containing combination medicines require a coordinated effort with pharmacy system software companies to overcome any existing challenges with field lengths designated for drug names. <p>Implement one standard acetaminophen warning label</p> <ul style="list-style-type: none"> • Opportunity to collaborate with the warning label companies and pharmacy system software companies to establish industry standard. • Explore opportunities to harmonize and standardize warning labels for other active ingredients to improve patient understanding of all warning labels provided on the same prescription container label of all acetaminophen-containing medicines, in collaboration with both pharmacy system software and warning label companies. <p>Education and communication with healthcare professionals and patients</p> <ul style="list-style-type: none"> • Collaborate with both pharmacy system and other stakeholders to find synergies and seek innovative solutions to improve patient education and communication at point-of-dispensing and point-of-use.

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Stakeholders	Call to Action	Challenges and Opportunities
Pharmacy System Software Companies	<ol style="list-style-type: none"> 1. Complete spelling of acetaminophen and other active ingredients. <ul style="list-style-type: none"> • Eliminate “APAP” and abbreviations or truncated versions for acetaminophen spelling from data files of all acetaminophen-containing medicines. • When a brand or branded generic is dispensed, acetaminophen should be completely spelled in addition to the brand or branded generic name on prescription container labels. (Section 6.1) • Assign appropriate field length to allow complete spelling of “acetaminophen” and all other active ingredients on prescription labels for all acetaminophen-containing medicines. 2. Adopt one standard warning label for all acetaminophen-containing prescription medicines, utilizing the concepts presented in this white paper. (Section 6.2) <ul style="list-style-type: none"> • Standardize prioritization of print sequence for the new standard acetaminophen warning label to print among the top three pharmacy warning labels. • Delete all warning labels containing similar key messages from warning label data files, to prevent duplication of key messages on prescription labels. 	<p>Complete spelling of acetaminophen and other active ingredients</p> <ul style="list-style-type: none"> • Collaborate with drug database publishers on the timing of system change for complete spelling of all active ingredients in order to overcome any existing spacing challenges of drug name fields. <p>Implement one standard acetaminophen warning label</p> <p>Opportunity to collaborate with the warning label companies and drug database publishers to:</p> <ul style="list-style-type: none"> • Adopt one standard acetaminophen warning label aligned with the FDA approved warnings for OTC Drug Facts labels. • Develop the new standard warning label in a patient-centered manner, applying plain language and health literacy principles. • Standardize print sequence for these labels to ensure printing of acetaminophen warning labels within the top three of warning labels. • Explore opportunities to harmonize and standardize warning labels for other active ingredients to improve patient understanding of all warning labels provided on same prescription container label of all acetaminophen-containing medicines, in collaboration with both drug database publishers and warning label companies. <p>Education and communication with healthcare professionals and patients</p> <ul style="list-style-type: none"> • Collaborate with both drug database publishers, pharmacy software companies and other stakeholders to find synergies and seek innovative solutions to improve patient education and communication at point-of-dispensing and point-of-use.

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Stakeholders	Call to Action	Challenges and Opportunities
Pharmacy Warning Label Companies	<ol style="list-style-type: none"> 1. Adopt content for new standard acetaminophen-ingredient warning label and ensure warning label is developed in a patient-centered manner, utilizing appropriate and optimized font size. 2. Delete all warning labels containing similar key messages from warning label data files to prevent duplication of key messages on prescription labels. 	<p>Implement one standard warning label</p> <p>Opportunity to collaborate with the warning label companies and drug database publishers to:</p> <ul style="list-style-type: none"> • Develop an industry standard warning label for acetaminophen-containing prescription medicines, in collaboration with colleagues. • Consider including one standardized acetaminophen-ingredient icon across industry to further help patient recognition of acetaminophen as active ingredient. • Explore opportunities to harmonize and standardize warning labels for other active ingredients to improve patient understanding of all warning labels provided on the prescription container of acetaminophen-containing medicines, in collaboration with both drug database publishers and pharmacy system software companies.
Pharmacy	<ol style="list-style-type: none"> 1. Adopt the proposed labeling changes for all acetaminophen-containing medicines dispensed in pharmacy. 2. Collaborate with pharmacy system software company(ies) to incorporate the labeling changes recommended in this white paper. 3. Optimize pharmacist-patient counseling, communication and education at point-of-dispensing and point-of-use. <ul style="list-style-type: none"> • Alert pharmacy staff of importance of pointing out acetaminophen in addition to opioids and other active ingredients. 	<p>Education and communication with healthcare professionals and patients</p> <ul style="list-style-type: none"> • Seek synergies and innovative solutions to improve patient education and communication at point-of-dispensing and point-of-use through collaboration with both pharmacy system, as well as other stakeholders.

8. Conclusions

Even though rare in the context of its widespread use, liver injury from acetaminophen overdose remains a serious public health problem and lack of patient awareness regarding the content of their prescription medicines has been identified as a contributing factor to unintentional overdose. To improve patients' appropriate use of acetaminophen-containing medicines and patient safety, consumers and patients need to be able to read labels and recognize when their medicines contain acetaminophen. Improving current prescription labeling of acetaminophen-containing medicine needs to be made a priority.

The recommended best practices take into consideration existing regulations and authorities, in addition to the standards recommended by experts who have addressed patient-centered approaches to labeling in order to maximize readability and patient comprehension. For instance, the OTC Drug Facts label regulations, NABP Model Act and USP's Chapter <17> proposal for standardizing prescription labels employ health literacy principles and utilize or recommend a standard format. In the case of the OTC Drug Facts label, the public is already familiar with the format. Harmonization with existing standards and recommendations such as these can help the pharmacy system industry implement labeling that can improve patient safety.

Efforts by stakeholders conducting regulatory and education initiatives to decrease harm caused by accidental overdoses from acetaminophen-containing medicines are ongoing. While these efforts are essential and important ways to impact patient safety, these efforts alone are not enough to improve patient safety. Other non-regulatory, voluntary, parallel efforts are needed to potentiate the effect of those efforts.

Implementation of the recommendations in this white paper is the essential first step towards making it possible for patients to identify and compare active ingredients on their prescription and OTC medicine labels and to avoid taking two medicines which contain acetaminophen simultaneously. Voluntary efforts by the pharmacy system industry to improve prescription container labels for acetaminophen-containing medicine not only provide consistency across OTC and prescription container labels but also across state lines, decreasing the variability that results when states take individual regulatory paths to standardization.

The NCPDP "Acetaminophen Best Practices" Task Group Call to Action is first and foremost directed to all pharmacy system stakeholders who are well positioned to play a critical role in supporting and driving development of patient-centered prescription container labels and implementing sustainable change and improvement. Additional steps needed are:

- An NCPDP strategy for dissemination of the white paper to engage all key stakeholders.
- The white paper syndication to all stakeholders who currently play a critical role in educating healthcare professionals, consumers and patients on appropriate use of medicines.
- Additional concerted efforts from other stakeholders to optimize healthcare professional, consumer and patient communication.

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- A second call to action to all pharmacy system stakeholders, publishers of drug databases, commercial and proprietary system software companies and warning label companies to further explore implementation of innovative patient-centered communication and education solutions that target and encourage pharmacist-to-patient conversations and education at point-of-dispensing, utilizing their state of the art clinical decision-support module systems.

All stakeholders are encouraged to enter into a dialogue to find synergies to utilize existing programs and collaborate on future initiatives.

9. References

- 21 CFR §201 Subpart B Labeling Requirements for Prescription Drugs and/or Insulin
- 21 CFR §201.57 (c)(1) Specific requirements on content and format of labeling for human prescription drug and biological products described in 201.56(b)(1)
- 21 CFR §201.61 Statement of identity
- 21 CFR §201.66(c)(2) and (3) Format and content requirements for over-the-counter (OTC) drug product labeling
- 21 CFR §201.326, Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required warnings and other labeling
- 21 CFR §290.5 Drugs; statement of required warning
- 21 CFR §299.4 Established names for drugs
- 21 CFR §1306.24 Labeling of substances and filing of prescriptions
- 21 USC §353 (b)(2) Exemptions and consideration for certain drugs, devices, and biological products ((b) Prescription by physician; exemption from labeling and prescription requirements; misbranded drugs; compliance with narcotic and marihuana laws)
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10. Appendices

NCPDP Recommendations for Improved Prescription Container Labels
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10.1 Appendix A: Survey of Current Acetaminophen Warning Labels

	Warning Label Company			Warning Label: Full Text	Key Messages
Label	A	B	C		
1				This medicine contains ACETAMINOPHEN. Taking more than recommended may cause liver problems. Ask your doctor before taking other products containing ACETAMINOPHEN.	Content, Overdose, Liver warning, Concomitant use
2				This medicine contains ACETAMINOPHEN. Taking more ACETAMINOPHEN than recommended may cause serious liver problems.	Content, Overdose, Liver warning
3				This medicine contains ACETAMINOPHEN. Taking more ACETAMINOPHEN (PARACETAMOL) than recommended may cause serious liver problems.	Content, Overdose, Liver warning
4				This medicine contains ACETAMINOPHEN. Taking more than 4000 mg of Acetaminophen per day may cause serious liver problems.	Content, Overdose, Liver warning
5				Do not take ACETAMINOPHEN containing products at the same time without first checking with your doctor. Check all medicine labels carefully.	Concomitant use
6				Do not take other ACETAMINOPHEN containing products at the same time without first checking with your doctor. Check all medicine labels carefully.	Concomitant use
7				Do not take other ACETAMINOPHEN (PARACETAMOL) containing products at the same time without first checking with your doctor. Check all medicine labels carefully.	Concomitant use
8				Do not take aspirin or acetaminophen without checking with your doctor or pharmacist.	Other

NCPDP Recommendations for Improved Prescription Container Labels
for Medicines Containing Acetaminophen

10.2 Appendix B: Sample Acetaminophen Drug Facts Label Excerpt

Over-the Counter *Drug Facts* Label

Selected Sections for Acetaminophen Single Ingredient Over-the-Counter Medicine Labeled for Adult Use Only

Drug Facts	
Active ingredient (in each tablet)	Purpose
Acetaminophen XXX mg.....	Pain reliever/fever reducer
Uses	
<ul style="list-style-type: none">■ temporarily relieves minor aches and pains due to:<ul style="list-style-type: none">■ the common cold■ headache■ backache■ minor pain of arthritis■ toothache■ muscular aches■ premenstrual and menstrual cramps■ temporarily reduces fever	
Warnings	
<p>Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take</p> <ul style="list-style-type: none">■ more than X tablets in 24 hours, which is the maximum daily amount■ with other drugs containing acetaminophen■ 3 or more alcoholic drinks every day while using this product	
Do not use	
<ul style="list-style-type: none">■ with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.	

Reference Sections 5.1.2 and 5.1.3 of this White Paper for written description of Drug Facts label regulations.

Note that acetaminophen is completely spelled out in “**Active ingredient**” section of the Drug Facts label, as recommended for the prescription label in Section 6.1 of this White Paper. Note the “**Warnings**” section of the Drug Facts label contains the four elements recommended and described for the prescription pharmacy warning label in Section 6.2 of this White Paper.

NCPDP Recommendations for Improved Prescription Container Labels
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10.3 Appendix C: Sample Acetaminophen Prescription Container Label ⁴⁶

Adopt one standard warning label for all acetaminophen-containing prescription medicines.

Standardize prioritization of print sequence to print among the top three pharmacy warning labels.

Always completely spell “acetaminophen” and all other active ingredients on the prescription label.

No abbreviation, acronym or truncated version of any active ingredient should be permitted on a prescription label.

The image shows a sample prescription container label for a medicine containing acetaminophen. The label is divided into several sections. On the left, there are three warning labels: 'May cause drowsiness. Use care when operating a car or dangerous machines. Don't drink alcohol when taking this medicine.', 'This has acetaminophen. Don't take with other medicines that have acetaminophen (prescription or nonprescription). Too much can cause liver damage. Questions? Ask your doctor or pharmacist.', and 'Taking more of this medicine than recommended may cause serious breathing problems.' Below these are dates: 'Orig: 10/31/2011', 'Date Filled: 10/31/2011', 'Discard after: 10/31/2012', and a description: 'This is a white, oval-shaped tablet with no imprint'. At the bottom left is a caution: 'CAUTION: FEDERAL LAW PROHIBITS THE TRANSFER OF THE DRUG TO ANY PERSON OTHER THAN THE PATIENT FOR WHOM WAS PRESCRIBED.' In the center is a vertical barcode. On the right, the pharmacy name 'Local Pharmacy' is at the top, followed by the address '1234 Winding Street, Fort Washington, PA 12345'. Below that is the patient's name 'John Smith' and address '3254 Maple Street, Fort Washington, PA, 12345'. The 'Brandname' section is highlighted with a red box and contains 'hydrocodone/acetaminophen' and 'X mg / XXX mg'. Below this is the dosage instruction 'Take 1 tablet by mouth every 4-6 hours as needed for pain'. Further down are fields for 'Qty: 30' and 'Refills: 0'. Below that is the 'Pharmacy Phone: (609) 555-5562' and 'Rx # A123456'. At the bottom right is the 'Prescriber: Dr. Johnson'.

May cause drowsiness. Use care when operating a car or dangerous machines. Don't drink alcohol when taking this medicine.

This has acetaminophen. Don't take with other medicines that have acetaminophen (prescription or nonprescription). Too much can cause liver damage. Questions? Ask your doctor or pharmacist.

Taking more of this medicine than recommended may cause serious breathing problems.

Orig: 10/31/2011
Date Filled: 10/31/2011
Discard after: 10/31/2012

This is a white, oval-shaped tablet with no imprint

CAUTION: FEDERAL LAW PROHIBITS THE TRANSFER OF THE DRUG TO ANY PERSON OTHER THAN THE PATIENT FOR WHOM WAS PRESCRIBED.

Local Pharmacy
1234 Winding Street
Fort Washington, PA 12345

John Smith
3254 Maple Street Fort Washington, PA, 12345

Brandname
hydrocodone/acetaminophen
X mg / XXX mg

Take 1 tablet by mouth every 4-6 hours as needed for pain

Qty: 30 Refills: 0

Pharmacy Phone: (609) 555-5562

Rx # A123456

Prescriber: Dr. Johnson

⁴⁶ The information presented here is not intended to support or imply standard formatting or language to be used on a prescription label.

10.4 Appendix D: Contributors to this White Paper

Note: the organizations listed below should not be considered endorsers of this White Paper.

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